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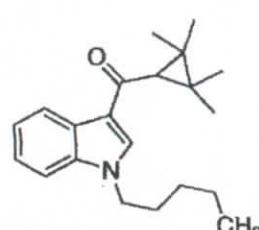
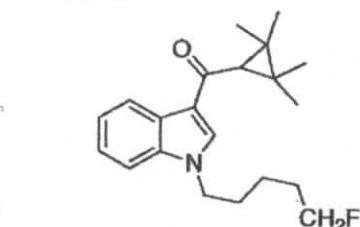
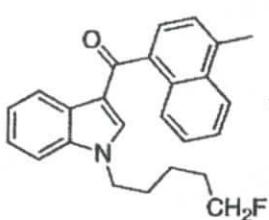
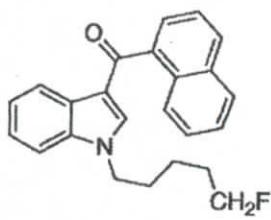
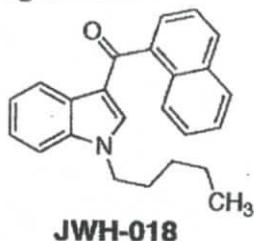
SCHOOL OF SCIENCE
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May 10, 2013

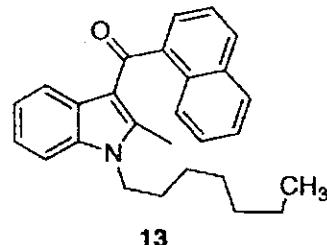
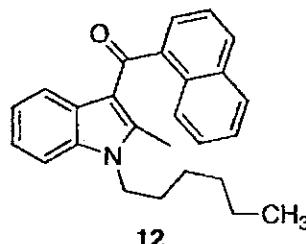
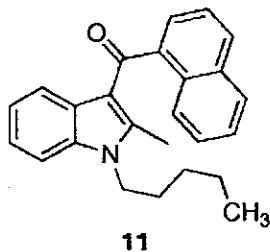
Dr. James E. Felman
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Dear Dr. Felman:

UR-144, XLR-11, AM-2201, and MAM-2201 are not analogues of JWH-018 under the Federal Analogue Act when careful analysis of structural features of the four compounds is compared with those of JWH-018. My conclusions are made with the assistance of data from additional compounds with the same functional groups that are part of UR-144, XLR-11, AM-2201, and MAM-2201. The structural changes on the indole nucleus clearly differentiate these four compounds from JWH-018, as I will demonstrate. My explanations prevent inaccurate decisions on classifications that unfortunately could result from a non-scientific interpretation of the vague definition of analogue in the Federal Analogue Act.



With regard to XLR-11, AM-2201, and MAM-2201 that incorporate fluoride on the C-terminal carbon of the n-pentyl group, the molecules can be classified as heteroarylalkyl fluorides. Introduction of even just a single fluoride into a molecule can substantially change the new molecule and make it confusing if the classification of the fluoride-containing molecule is not



In summary, it has been demonstrated why UR-144, XLR11, AM2201, and MAM2201 are not analogues of JWH-018 under the Federal Analogue Act and an example of a compound was shown that is an analogue but does not bind to the CB1 receptor ($K_i > 10,000$ nM). It is important to note that many compounds with an indole nucleus, as part of the structure, have a number of different biological activities but having an indole as part of the structure does not make the compound an analogue and that even very close analogues may not have similar biological activities. I will be more than happy to expand on my comments and discuss in detail my rationale for these conclusions.

Sincerely,

James R. McCarthy, Ph.D.

Professor

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References

1. Baker, C. H.; Banzon, J.; Bollinger, J. M.; Stubbe, J.; Samano, V.; Robins, M.J.; Lippert, B.; Jarvi, E.; Resvick, R. *J. Med. Chem.* 1991, **34**, 1879-1884.
2. Carrel, H.L.; et al *Science*, 1970, 1170, 1412.
3. (a) Rosita, D.; DeWit, M. A.; Luyt, L. G. *J. Med. Chem.* 2009, **52**, 2196-2203. (b) Luyt, L. G. Private communication.
4. McCarthy, J. R.; Robins, R.K.; Robins, M. J. *J. Am. Soc.* 1968, **90**, 4993-4999.
5. McCarthy, J.R.; Jarvi, E.T.; Matthews, D.P.; Edwards, M.L.; Prakash, N.J.; Bowlin, T.L.; Mehdi, S.; Sunkara, P.S.; Bey, P. *J. Am. Chem. Soc.* 1989, **111**, 1127-1128.
6. Gordon, A. J. *J. Chem Educ.* 1967, **44**, 461-464.
7. Bender, D. M.; Peterson, J. A.; McCarthy, J. R.; Gunaydin, H.; Takano, Y.; Houk, K. N. *Org. Lett.* 2008, **10**, 509-511.
8. Wiley, J.L.; Compton, D.R.; Dal, D.; Lainton, J.A.H.; Phillips, M.; Huffman, J.W.; Martin, B.R. *J. Pharm. Expt. Ther.* 1998, **285**, 995-1004.
9. De Sa Alves, F. R.; Barreiro, E.J.; Fraga, C.A.M. *Mini-Reviews in Med Chem.* 2009, **9**, 782-793.